ladium catalyst are (1) oxidative addition of acyl chlorides to palladium(0), (2) transmetalation of organostannane, and (3) reductive elimination of the product. The oxidative addition of arylsulfonyl chlorides to platinum(0), rhodium(I), and palladium(II) complexes is well documented.[10-12] Although there is no documentation on the transmetalation and subsequent reductive elimination with the formation of a C–S bond, these same intermediate steps could be proposed for the catalytic cycle. The mechanism for the self-coupling of organostannanes is not yet clear.

The following procedure for the coupling of (*E*)-styryltributylstannane with *p*-toluenesulfonyl chloride is representative. To a solution of *p*-toluenesulfonyl chloride (200 mg, 1.0 mmol) in 5 mL of dry THF was added (*E*)-styryltributylstannane (430 mg, 1.1 mmol) followed by tetrakis(triphenylphosphine)palladium(0), **1** (12 mg, 1.0 mol %). The resulting pale yellow solution was heated at 65–70 °C for 15 min with stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and treated with an excess of aqueous KF for 2–3 h with vigorous stirring. The precipitated tin fluoride complex was removed by filtration and was washed well with ethyl acetate. The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the residue was purified by flash chromatography to give (*E*)-styryl *p*-toluyl sulfone (0.19 g, 77%): mp 121–122 °C (hexane/EtOAc, lit.[13] mp 121–122 °C).

In summary, a general, single-step method for the preparation of vinyl- and allylsulfones was developed. This palladium-catalyzed cross-coupling reaction proceeds to provide good to excellent yields of sulfones and is highly catalytic. The reaction, however, is limited to the substituted alkenyl- and allylstannanes. The palladium-catalyzed self-coupling of the organostannanes, which has not been previously reported, is noteworthy and further investigation of this aspect is under way. In this paper, we have shown that the palladium-catalyzed coupling reactions of substituted vinyl- and allylstannanes can be applied in the C–S bond formation, as well.

(13) Truce, W. E.; Simms, J. A.; Hill, H. E. *J. Am. Chem. Soc.* **1953**, *75*, 5411.

Total Synthesis of K-13

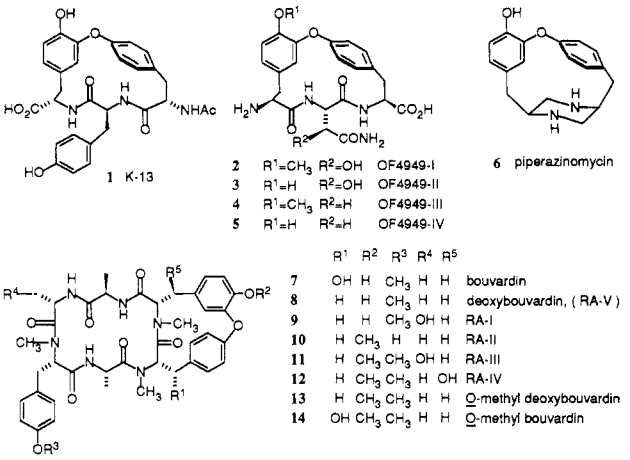
Dale L. Boger*[18a] and Daniel Yohannes[18b]

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

Received February 17, 1989

Summary: A total synthesis of K-13 (1), an isodityrosine-derived cyclic tripeptide possessing potent noncompetitive angiotensin I converting enzyme inhibitory activity, is detailed.

Sir: K-13 (1), an isodityrosine-derived cyclic tripeptide isolated from *Micromonospora halophytica* subsp. *exilisia K-13* and identified by spectroscopic and chemical degradative studies,[1] has been shown to be a potent, noncompetitive inhibitor of angiotensin I converting enzyme (I_{50} = 0.17 μg/mL, K_i = 0.35 μM) and a weak inhibitor of aminopeptidase B.[2] Consequently, K-13 represents the newest addition to a class of biologically active isodityrosine-derived[3] cyclic peptides now including OF4949-I–OF4949-IV (**2–5**),[4] piperazinomycin (**6**),[5] and a growing class of bicyclic hexapeptide antitumor–antibiotics **7–14**.[6]



(1) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

(2) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455.

(3) Isodityrosine: (a) Fry, S. C. *Biochem. J.* **1982**, *204*, 449. (b) Cooper, J. B.; Varner, J. E. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 161.

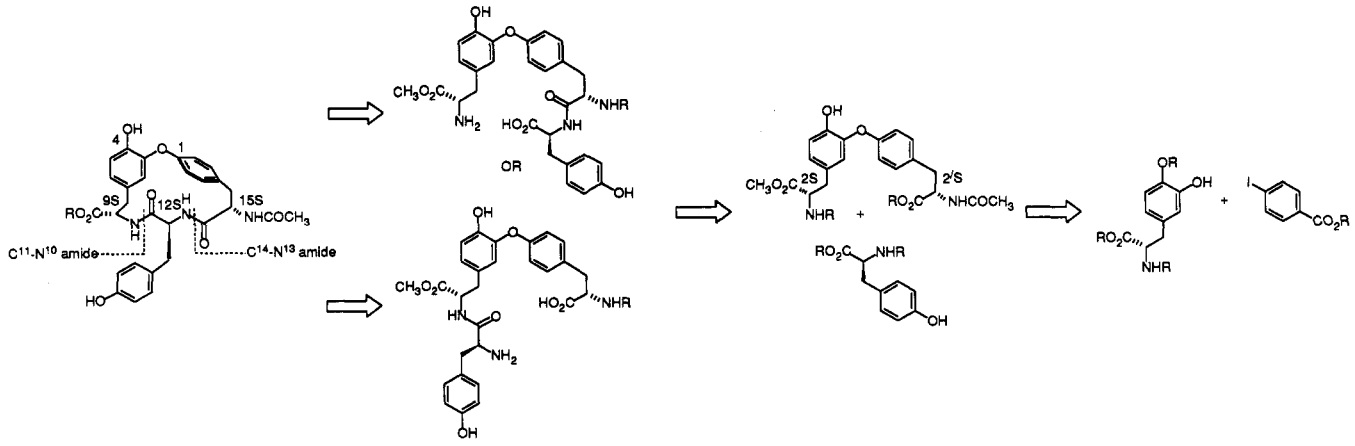
(4) OF4949-I–OF4949-IV. Fermentation, isolation, and characterization: (a) Sano, S.; Ikai, K.; Kuroda, H.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1674. Structure elucidation: (b) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685. Biosynthesis: (c) Sano, S.; Ueno, M.; Katayama, K.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1986**, *39*, 1697. Total synthesis: (d) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. (e) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227.

(5) Piperazinomycin. Fermentation, isolation, characterization, and biological properties: Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130. X-ray structure determination: Kaneda, M.; Tamai, S.; Nakamura, S.; Hirata, T.; Kushi, Y.; Suga, T. *J. Antibiot.* **1982**, *35*, 1137. Total synthesis: Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. Synthetic studies: Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.

(6) (a) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. (b) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T. ; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762. Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424. Itokawa, H.; Takeya, K.; Mori, N.; Kidokoro, S.; Yamamoto, H. *Planta Med.* **1984**, *51*, 313. (c) Natural and synthetic derivatives of RA bicyclic hexapeptides: Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Chem. Pharm. Bull.* **1984**, *32*, 3216. Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann.* **1984**, *75*, 929. Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 284. (d) Total synthesis: Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957. (e) Synthetic studies and key partial structures: Bates, R. B.; Gin, S. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kreik, G. R.; Michaud, J.-P.; Vine, D. B. *Heterocycles* **1984**, *22*, 785. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487. Inoue, T.; Naitoh, K.; Kosemura, S.; Umezawa, I.; Sonobe, T.; Serizawa, N.; Mori, N.; Itokawa, H. *Heterocycles* **1983**, *20*, 397.

0022-3263/89/1954-2498$01.50/0

Scheme I



Herein we detail a total synthesis of K-13 (1) and its structural confirmation including an unambiguous establishment of its absolute configuration[7] based on the implementation of an Ullmann condensation reaction that may be conducted without amino acid racemization and that has proven suitable for incorporation of a selectively-protected catechol including derivatives of L-Dopa, e.g. **15**. Additional studies on the key macrocyclization reaction leading to 17-membered cyclic tripeptides incorporating a diaryl ether linked meta- and paracyclophane structrual subunit are detailed, Scheme I.

Ullmann condensation of the selectively protected L-Dopa derivative **15**[8] (L:D 95:5)[9a] with *tert*-butyl *p*-iodobenzoate (**16a**, NaH, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130 °C, 8 h, 46%) provided the diaryl ether **17** (L:D 94:6)[9a] under reaction conditions that permitted the coupling to proceed *without* amino acid racemization[4e] and permitted the use of the phenol **15** consituting part of a selectively protected catechol, Scheme II.[10] Conversion of the *tert*-butyl ester **17** to the carboxylic acid **18** (3.0 M HCl/EtOAc, 25 °C, 1.5 h, 95%) and subsequent reduction ($BH_3{\cdot}THF$, THF, 0 °C, 3 H, 89%) provided the primary alcohol **19**, which was converted to primary bromide **20** (CBr_4, Ph_3P, Et_2O, 25 °C, 72%). Alternatively, the carboxylic acid **18** could be obtained directly from the Ullmann condensation reaction of **15** with sodium *p*-iodobenzoate (**16b**, NaH, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130 °C, 8 h, 51%). Treatment of benzyl bromide

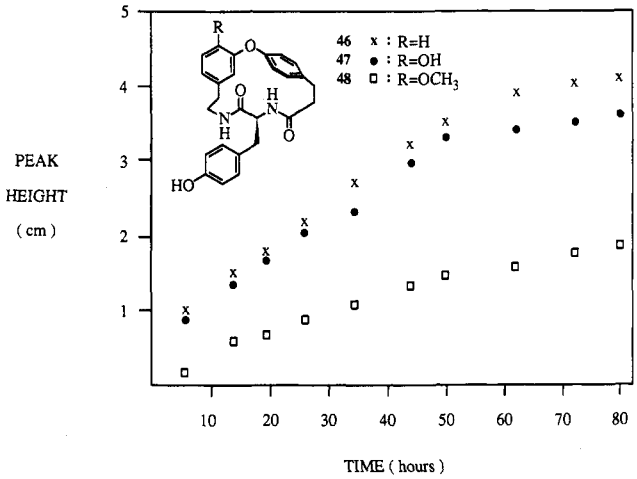


Figure 1. Plot of normalized peak heights (HPLC separation, UV detection) of the products (**46**, **47**, **48**) of cyclization of a 1:1:1 mixture of **49**:**50**:**51** versus time (1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0.008 M, 0 °C) illustrating the comparable rates of macrocyclization of **46** and **47** and the substantially slower rate of cyclization of **48**, supplementary material. The k_{rel} = **46** (1.0), **47** (0.94), **48** (0.40).

20 with Schöllkopf's reagent **21**[11] (NaH, THF, 0 °C, 5 min; **21**, THF, −78 °C, 14 h) and subsequent acid-catalyzed hydrolysis of the cyclic imidate **22** (0.5 N aqueous HCl/THF, 25 °C, 15 h, 57% from **20**) provided **23**.[9b]

Directed hydrolysis of the C-2′ methyl ester was accomplished through conversion of free amine **23** to the trifluoroacetamide **24** ($(CF_3CO)_2O$, THF, 25 °C, 1 h, 97%). Intramolecular, base-catalyzed closure of **24** (NaH, THF, 0 °C → 25 °C, 67%) to the corresponding unstable oxazolidinone provided the carboxylic acid **25** upon hydrolytic aqueous workup.[12] This directed and selective intramolecular hydrolysis of the C-2′ methyl ester proved sufficiently mild to proceed *without* racemization of the C-2′ center.[9c,12] Removal of the trifluoroacetamide (K_2CO_3, $MeOH/H_2O$ (5:2), 25 °C, 6 h, 86%) followed by *tert*-butyloxycarbonyl carbamate formation ($(t\text{-}BuO_2C)_2O$, K_2CO_3, THF, 25 °C, 2 h, 91%) provided **27** that was coupled directly to [2-(trimethylsilyl)ethyl]-L-tyrosine (EDCI, CH_2Cl_2, 25 °C, 9 h, 85%) to provide the fully protected linear tripeptide **28**. 2-(Trimethylsilyl)ethyl ester removal (*n*-Bu_4NF, DMF, 25 °C, 4 h, 92%) afforded **29** and diphenyl phosphoroazidate promoted cyclization of the free amine

(7) (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (b) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379. As detailed herein, we independently established the absolute configuration of K-13 as 9*S*,12*S*,15*S*-**1**.

(8) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1987**, *52*, 5283.

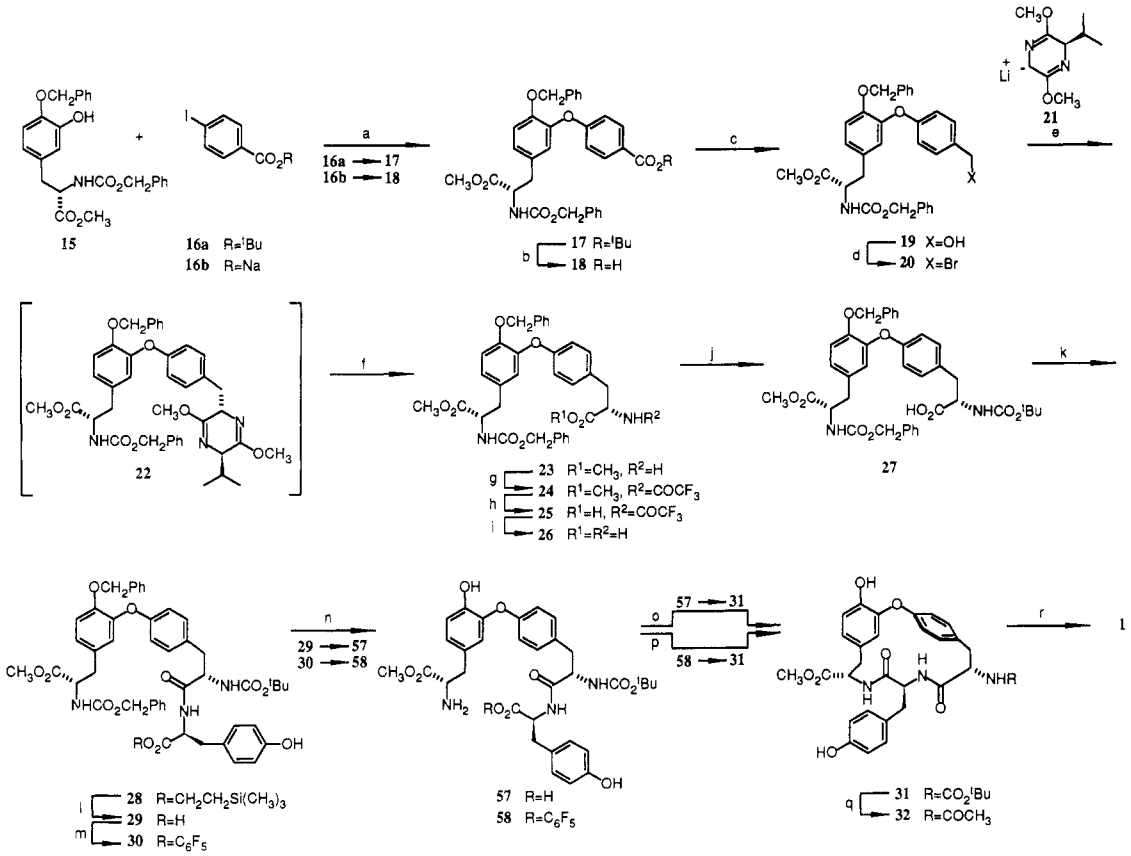
(9) HPLC analysis was performed on a Gilson Model 320 dual pump chromatograph equipped with an ISCO V[4] variable wavelength absorbance detector. (a) Chrial-phase HPLC analysis employing a J. T. Baker Bakerbond DNPG (covalent) chiral column revealed a 94:6 ratio of L:D-**17**; t_R : 21 min/23 min, 2.0 mL/min, 10% 2-propanol–hexane from reaction of a 95:5 ratio of L:D-**15**; t_R = 18 min/28 min, 2.0 mL/min, 10% 2-propanol–hexane. (b) Normal-phase HPLC analysis employing an Alltech Econosil silica column (10 μ) of the *N*-(*tert*-butyloxycarbonyl) derivative of **23** revealed a 90:4.5:4.5:<1 ratio of diastereomers; t_R = 15 min/17 min/18 min/20 min, 1.5 mL/min, 15% 2-propanol–hexane. (c) Normal-phase HPLC analysis employing an Alltech Econosil silica column (10 μ) of the product of diazomethane treatment of **25** revealed a single peak with an identical retention time (t_R = 15.2 min) to that obtained for **24** (t_R = 15.2 min; 2.0 mL/min, 25% EtOAc–hexane).

(10) In contrast to the independent and related efforts of Schmidt,[4e] we have observed substantial racemization of **15** and **17**–**18** (supplementary material) if the Ullmann condensation is conducted under standard reaction conditions (pyridine, 130 °C, 8–18 h, ca 90% racemization). The apparent difference in the observations may be due to the diminished acidity of a *tert*-butyl ester relative to a methyl ester. Boger, D. L.; Yohannes, D. *Tetrahedron Lett*, in press.

(11) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.

(12) Efforts to employ the acetamide derivative failed to close cleanly and rapidly to the intermediate oxazolidinone and suffered competitive racemization.

Scheme II[a]



[a] (a) 1.0 equiv of NaH, 1.4 equiv of $CuBr \cdot SMe_2$, $C_6H_5NO_2$, 130 °C, 8 h; 46% for **17**, 51% for **18**; (b) 3.0 M HCl/EtOAc, 25 °C, 1.5 h, 95%; (c) 1.0 equiv of $BH_3 \cdot THF$, THF, 0 °C, 3 h, 89%; (d) 2.0 equiv of CBr_4, 2.0 equiv of Ph_3P, Et_2O, 25 °C, 72%; (e) 1.0 equiv of NaH, THF, 0 °C, 5 min; 1.0 equiv of **21**, THF, −78 °C, 14 h; (f) 0.5 N aqueous HCl/THF (1:1), 25 °C, 15 h, 57% from **20**; (g) 1.05 equiv of $(CF_3CO)_2O$, THF, 25 °C, 1 h, 97%; (h) 1.0 equiv of NaH, THF, 0 °C → 25 °C, 68%; (i) 10% K_2CO_3/MeOH–H_2O (5:2), 25 °C, 6 h 86% (j) 1.05 equiv $(t\text{BuOCO})_2O$, 2.0 equiv of K_2CO_3, THF, 25 °C, 2 h, 91%; (k) 1.0 equiv of [2-(trimethylsilyl)ethyl]-L-tyrosine, 1.0 equiv of EDCI, CH_2Cl_2, 25 °C, 9 h, 85%; (l) 1.0 equiv of *n*-Bu_4NF, DMF, 25 °C, 4 h, 92%; (m) 1.0 equiv of EDCI, 2.0 equiv of C_6F_5OH, CH_2Cl_2, 25 °C, 2 h 85%; (n) 10 wt equiv of 10% Pd–C, 1 atm of H_2, 2.0 equiv of 10% HCl(aq), THF, 25 °C, 4 h; (o) 1.5 equiv of DPPA, DMF, 0.008 M, pH 7 ($NaHCO_3$), 0 °C, 72 h, 61%; (p) DMF addition (18 h) to DMF containing 5 equiv of $NaHCO_3$, 0.0003 M final concentration; 90 °C, additional 2 h, 51%; (q) 3.0 M HCl/EtOAc, 25 °C, 2 h; 1.05 equiv of $(CH_3CO)_2O$, 3.0 equiv of $NaHCO_3$, THF, 25 °C, 2 H, 89%; (r) 2.5 equiv of $LiOH \cdot H_2O$, THF/MeOH/H_2O (3:1:1), 25 °C, 4 h, 93%.

employing the recently improved reaction conditions[13] (10% Pd–C, 1 atm of H_2, 2.0 equiv of aqueous HCl/THF; 1.5 equiv DPPA, $NaHCO_3$, DMF 0.008 M, pH 7, 0 °C, 72 h, 61%) provided the cyclic tripeptide **31**. Alternatively, the carboxylic acid **29** was converted to the pentafluorophenyl active ester **30** (C_6F_5OH, EDCI, CH_2Cl_2, 25 °C, 2 h, 85%), and the corresponding free amine was subjected to high dilution cyclization reaction conditions (10% Pd–C, 1 atm of H_2, 2.0 equiv of aqueous HCl; slow addition (18 h, DMF) to a DMF solution containing 5 equiv $NaHCO_3$, 0.0003 M final concentration, 90 °C, 51%) and provided the cyclic peptide **31** in comparable yield.[15]

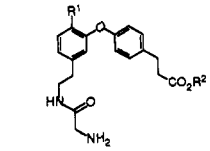
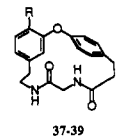
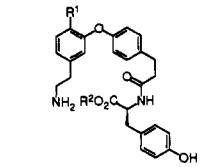
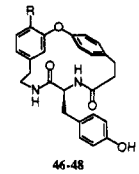
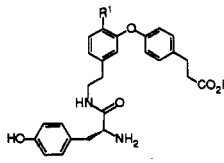
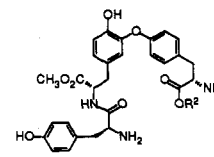
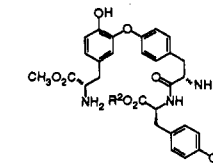
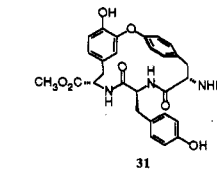
In the course of studies to promote the 17-membered macrocyclization reaction, two apparently unrelated substrate structural features proved to be key elements to the establishment of a successful ring closure reaction. The first, and anticipated, structural requirement was highlighted by unsuccessful efforts to promote the ring closure of acetamides **53** and **54** with formation of the C^{14}–N^{13} amide bond (Table I, entry 4). Presumably, intramolecular active ester closure to a 5-membered oxazolidinone proved competitive with the 17-membered ring closure reaction thus precluding C^{14}–N^{13} amide bond formation. This was apparently confirmed with the quantitative recovery of the free carboxylic acid **53** from the attempted cyclization of active ester **54** (Table I, entry 4c). However, initial attempts to promote the macrocyclization of acetamides **55** and **56** under comparable reaction conditions failed to provide cyclic tripeptide and do not suffer from an available competitive oxazolidinone ring closure reaction pathway (Table I, entries 5a,b). Thus, although the origin of the failure or rate deceleration of the macrocyclization of acetamides **55** and **56** is not obvious, it does suggest that a carbamate derivative of the C-15 amine would be perferred or required for observation of the 17-membered macrocyclization. More unusual was the effect that a remote C-4 aryl substituent had on the 17-membered ring closure. In *three* separate series, simple substrates lacking a C-4 aryl substituent and those bearing a C-4 free phenol were found to undergo macrocyclization without event while the identical substrates bearing a C-4 methyl ether

(13) Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Colton, C. D.; Homnick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101.

(14) Corey, E. J.; Weigel, L. O.; Chamberlin, R. A.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613. Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916.

(15) Rich, D. H.; Bhatnagar, P.; Mathiaparanam, P.; Grant, J. A.; Tam, J. P. *J. Org. Chem.* **1978**, *43*, 296. Lagarias, J. C.; Houghton, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202. Kisfaludy, L.; Roberts, J. E.; Johnson, R. H.; Mayers, G. L.; Kovacs, J. *J. Org. Chem.* **1970**, *35*, 3563.

Table I

entry	compd	R^1	R^2	precursor[a]	cyclization method (specific conditions)[b]	yield, %	compd	R	cyclic peptide
1a	**33**	H	H		A	71	**37**	H	 37-39
1b	**34**	OH	H		A	68	**38**	OH	
1c	**35**	OCH_3	H		A	66	**39**	OCH_3	
1d	**36**	OCH_3	C_6F_5		C	0	**39**	(88% recovered **35**)	
1e	**36**	OCH_3	C_6F_5		D	61	**39**	OCH_3	
2a	**40**	H	H		A	62	**46**	H	 46-48
2b	**40**	H	H		B	69	**46**	H	
2c	**41**	H	C_6F_5		C	49	**46**	H	
2d	**42**	OH	H		A	59	**47**	OH	
2e	**42**	OH	H		B	62	**47**	OH	
2f	**43**	OH	C_6F_5		C	57	**47**	OH	
2g	**44**	OCH_3	H		A	71	**48**	OCH_3	
2h	**45**	OCH_3	C_6F_5		C[c]	0	**48**	(88% recovered **44**)	
3a	**49**	H	H		A	68	**46**	H	
3b	**50**	OH	H		A	66	**47**	OH	
3c	**51**	OCH_3	H		A	12–25	**48**	OCH_3 (81–70% recovered **51**)	
3d	**51**	OCH_3	H		A (0.1 equiv of DMAP)	–	**48**	OCH_3 (100% recovered **51**)	
3e	**52**	OCH_3	C_6F_5		C	–	**48**	OCH_3 (96% recovered **51**)	
3f	**52**	OCH_3	C_6F_5		C (pyridine)[d]	53	**48**	OCH_3 (36% recovered **51**)	
3g	**52**	OCH_3	C_6F_5		D	58	**48**	OCH_3	
3h	**52**	OCH_3	C_6F_5		E	68	**48**	OCH_3	
4a	**53**	$COCH_3$	H		A	–	–	$COCH_3$ (oligomeric or cyclic polymer)	
4b	**53**	$COCH_3$	H		B	–	–	$COCH_3$ (oligomeric or cyclic polymer)	
4c	**54**	$COCH_3$	C_6F_5		C	–	**31**	$COCH_3$ (95% recovered **53**)	
5a	**55**	$COCH_3$	H		A	–	**31**	$COCH_3$ (100% recovered **55**)	 31
5b	**56**	$COCH_3$	C_6F_5		C	–	**31**	$COCH_3$ (62% recovered **55**)	
5c	**57**	$CO_2{}^tBu$	H		A	61	**31**	$CO_2{}^tBu$	
5d	**58**	$CO_2{}^tBu$	C_6F_5		C	51	**31**	$CO_2{}^tBu$	

[a] All cyclization substrates were employed as their hydrochloride salts. [b] Standard reaction conditions used for each cyclization method are as follows. Method A: diphenylphosphoryl azide (1.5 equiv), $NaHCO_3$ (5.0 equiv), DMF (0.008 M), 0 °C, 72 h, ref 13. Method B: *n*-Bu_4NOH (1.0 equiv), $C_6H_5CH_3$; mesitylsulfonyl chloride (3.0 equiv), iPr_2NH (3.0 equiv), C_6H_6, 35 °C, 48 h, ref 14. Method C: DMF (18 h addition, 0.0003 M final concentration), $NaHCO_3$ (5.0 equiv), DMF, 90 °C, additional 1 h, ref 15. Method D: (cyclization substrate employed as *N*-carbobenzyloxy derivative) dioxane (8 h addition, 0.001 M final concentration), H_2 (1 atm), Pd(0) (0.1 wt equiv), *N*-methylmorpholine (1.0 equiv), dioxane (1% absolute EtOH), ref 7. Method E: dioxane (12 h addition, 0.0004 M final concentration), dioxane-pyridine, 90 °C, additional 1 h, ref 7. [c] Higher (120 °C) reaction temperatures afforded the same result. [d] Rigorously dried pyridine was used as the reaction solvent with no additional $NaHCO_3$.

often failed a close productively to the 17-membered ring (Table I).[16] This proved most pronounced in the high dilution, thermal cyclization of the active pentafluorophenyl esters (Table I, entries 1c,d, 2g,h versus 2a–c and 2d–f, and 3e). On substrates comparable to those required for the total synthesis of K-13, this rate deceleration of the macrocyclization reaction proved substantial, Figure 1, and most pronounced in efforts to close the C^{14}–N^{13} versus C^{11}–N^{10} amide bond (Table I, entries 3 versus 2) but could be overcome by employing rigorously dried solvents in the pentafluorophenyl ester macrocyclization reaction (Table I, entry 3e versus 3f–h and 1d versus 1e).[16] Thus, the experimental observations suggest that the macrocyclization enroute to the preparation of K-13 is optimally conducted on substrates bearing a carbamate derivative of the C-15 amine and a free C-4 phenol with C^{11}–N^{10} amide bond closure. With such substrates, the macrocyclization reaction may be conducted uneventfully under established macrocyclization reaction conditions including the high dilution, thermal cyclization of an active pentafluorophenyl ester (Table I, entries 5c,d).[16]

(16) The failure to observe cyclization is due to competitive hydrolysis of the pentafluorophenyl esters attributable to the presence of adventitious water. This competitive hydrolysis was observed *only* with the slower cyclization reactions and can be avoided by employing rigorously dried solvents. Under such conditions, high yields of cycliztion products may by obtained from the cyclization of the refractory pentafluorophenyl esters. We thank Professor D. A. Evans for bringing this to our attention and sharing unpublished observations. There is, nonetheless, a modest to substantial rate deceleration (Figure 1) of the cyclization of substrates **35–36**, **44–45**, and **51–52** that may be attributed to the presence of the C-4 methoxy substituent.

(17) Synthetic (mp 264–268 °C) and natural K-13 (mp 265–70 °C) proved indistinguishable by ^1H NMR (CD_3OD and DMSO-d_6, 300 MHz), IR (KBr), and FABMS. The $[\alpha]_D$ for synthetic K-13, –5.6° (*c* = 0.53, CH_3OH), proved higher than that reported for natural K-13, –3.4° (*c* = 0.6, CH_3OH), and comparable to that independently recorded for synthetic K-13, –6.5° (*c* = 0.46, CH_3OH)[7a] and –7.4° (*c* = 0.65, CH_3OH).[7b] We thank Dr. Sano of Kyowa Hakko Kogyo Co., Ltd., Japan, for providing copies of spectra of naturally occurring K-13 [IR (KBr), SIMS and HRFABMS, ^1H NMR (CD_3OD and DMSO-d_6, 400 MHz), ^{13}C NMR (CD_3OD and DMSO-d_6, 100 MHz)].

(18) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA01134). Alfred P. Sloan research fellowship recipient, 1985–1989. (b) Purdue University Cancer Center fellowship recipient, 1988–1989.

Exchange of the *tert*-butyloxycarbonyl carbamate of **31** for the acetamide (3.0 M HCl/EtOAc, 25 °C, 2 h; $(CH_3CO)_2O$, $NaHCO_3$, THF, 25 °C, 2 h, 89% overall) followed by hydrolysis of the C-9 methyl ester ($LiOH \cdot H_2O$, THF/MeOH/H_2O, 25 °C, 4 h, 93%) provided K-13 ($[\alpha]^{22}_D$ −5.6° (*c* 0.53, methanol) natural $[\alpha]^{19}_D$ −3.4° (*c* 0.6, methanol)[2]), identical in all additional comparable respects with the naturally occurring material.[17]

Acknowledgment. This work was assisted by the financial support of the National Institutes of Health (Grant CA41101), the Alfred P. Sloan Foundation, and a Purdue University Cancer Center fellowship (D.Y.). We thank Professor D. A. Evans for providing us with details of their efforts in advance of publication (ref 7) and Dr. Sano for copies of spectra of naturally occurring K-13 (ref 16).

Supplementary Material Available: Experimental details and full spectroscopic and physical characterization of **1**, **17–20**, **23–32**, and the cyclic amides **37–39** and **46–48** are provided (15 pages). Ordering information is given on any current masthead page.

Highly Selective Formation of Cis-Substituted Hydroxylactams via Auxiliary-Controlled Reduction of Imides

Scott A. Miller and A. Richard Chamberlin*

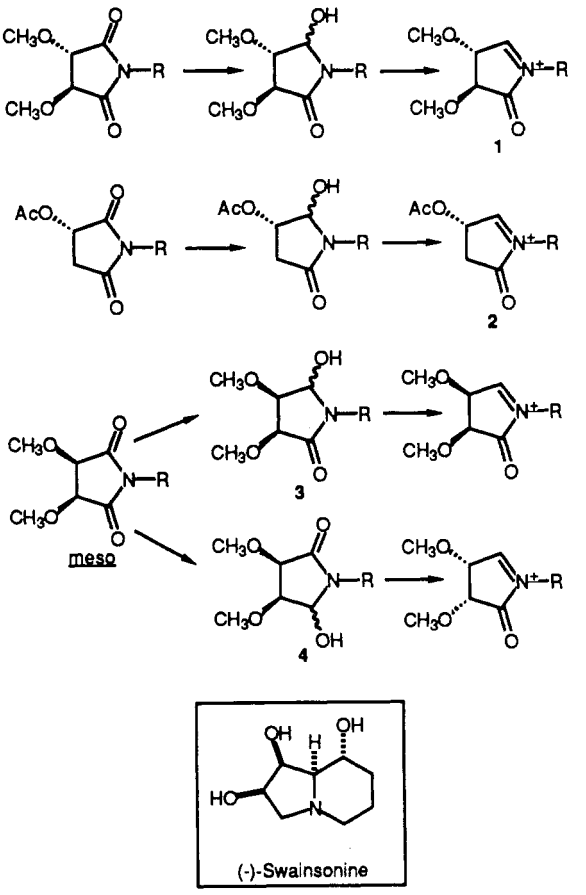
Department of Chemistry, University of California, Irvine, California 92717

Received March 8, 1989

Summary: A protected *cis*-dihydroxytartarimide with an appended chiral auxiliary undergoes highly selective reduction of either carbonyl group, affording acyliminium ion precursors that are not readily available by conventional imide reduction techniques.

Sir: Nucleophilic addition to acyliminium ions is a valuable method for the preparation of nitrogen-containing natural products.[1] One reason for the popularity of this reaction is that acyliminium ions are very convenient to prepare, via simple hydride reduction of cyclic imides[2] followed by elimination. While this reaction sequence has most often been carried out on simple achiral imides, enantiomerically pure chiral acyliminium ions such as **1** (Scheme I) can be generated from imides with C_{2v} symmetry (in which the carbonyl groups are chemically equivalent),[3] while monosubstituted derivatives such as **2** (Scheme I) have been prepared by regioselective reduction of unsymmetrical imides derived from malic acid.[4] This straightforward methodology is not applicable, however, to the enantioselective preparation of cis-substituted hydroxy lactams such as **3** or **4** because the corresponding starting material is a meso imide and thus would give racemic product. We have investigated several potential solutions to this interesting dilemma, which presents itself in iminium ion cyclization routes to glycosidase inhibitors such as swainsonine,[5] and in this communication we report our initial results on reductions directed by a stereogenic center attached at nitrogen.

Scheme I



For the initial studies, a chiral auxiliary was chosen so that several reduction modes could be examined: (a) intramolecular delivery of hydride, (b) chelation-controlled reduction (i.e., selective activation of one carbonyl group by auxiliary/metal/carbonyl chelation), and (c) sterically controlled reduction. The auxiliary selected based on these criteria was commercially available D-(−)-α-phenylglycinol,[6]

(1) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425 and references therein. (b) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235. (c) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 3963. (d) For a review of acyliminium cyclizations in alkaloid synthesis, see: Speckamp, W. N. *Recueil* **1981**, *100*, 345.

(2) (a) $NaBH_4$/ethanol/acid: Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. (b) $NaBH_4$/MeOH: Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (c) Diisobutylaluminum hydride: Hart, D. J.; Kanai, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.

(3) For examples, see: Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, 1987 and ref 1d.

(4) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (b) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(5) For a recent synthesis of (−)-swainsonine and references to previous syntheses, see: Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022.

(6) This compound serves as chiral auxiliary for a related transformation leading to lactones: Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385.

0022-3263/89/1954-2502$01.50/0